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Letter to the Editor

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First Pediatric Case of Autosomal Recessive Homozygotic Bestrophinopathy due to Homozygous Mutation c.187G>C p. in Two Brothers

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To the Editor

Autosomal recessive bestrophinopathy (ARB) is associated with mutations of the bestrophin-1 (BEST1) gene. BEST1 is one of four related genes that influence integral membrane proteins, called BEST1-4 genes, and were classified into five different classes (class I-V) [1]. The BEST1 mutation spectrum underlying bestrophinopathies involves over 300 known mutations [1-6]. In BEST1 gene mutations, gain-of-function and loss-of-function mutations occur [1, 5, 7]. The prevalence of autosomal recessive pattern of BEST1 mutation is described as 1:1,000,000 [8]. To date, there is no effective treatment of bestrophinopathies [7]. Prognosis of the different BEST mutations and their clinical features are not clearly definable [1, 5, 7, 8]. The pathology focuses on why BEST1 mutations disturb calcium-activated chloride channel activity with the result of retinal degeneration [2, 5, 9-12]. BEST1 mutations are normally autosomal dominant, but sometimes autosomal recessive and therefore as recessive entity indicative for ARB [7]. This genetic condition leads to different diseases of retinal degenerative disorders. ARB is rarely diagnosed compared to BEST1-associated autosomal dominant juvenile vitelliform macular degeneration (VMD) (Best's disease), which is not only due to its low prevalence (1:50,000), but also to the phenotypic differences to VMD [13-15]. Mutations in the BEST1 gene are causally associated with an increasing number of inherited ophthalmic diseases, which have collectively been termed "bestrophinopathies". These have initially included inherited retinal degenerative diseases, one of the most common inherited macular diseases, ARB, and autosomal dominant vitreoretinochoroidopathy (ADVIRC), among others. However, BEST1 mutations have also been implicated in more complex ophthalmic diseases with anterior segment involvement, namely autosomal dominant microcornea, rod-cone dystrophy, early-onset cataract, posterior staphyloma (MRCS) syndrome. ARB normally shows first clinical expression in the first two decades of life, but a few patients show first visual disturbances in the fifth decade of life. Mostly patients present with a central visual loss with a visual acuity range from 20/200 to 20/25 and show a hyperopic state. Additional ocular disturbances include a lower axial length with glaucoma, amblyopia and anterior uveitis. Strabismus and color vision defects are also found. Choroidal neovascularization (CNV) could also be an infrequent sign. Leukokoria and esotropia have also been described in literature. In addition, phenotypical differences have been noted between unrelated patients harboring the same mutation and also within families, including age of onset and rate of disease progression. This phenotypic and allelic heterogeneity highlights a significant phenotypic overlap among BEST1-linked disorders, which poses significant diagnostic and prognostic challenges. The pleiotropic effects of BEST1 gene mutations have raised the hypothesis that other unknown factors may play a role in bestrophinopathies, including genetic modifiers, BEST1 protein interactors, and environmental components. A decreased electro-oculographic (EOG) Arden ratio (light peak/dark trough) is a hallmark of all bestrophinopathies. This clinical finding has allowed further understanding of the biologic role of BEST proteins in the human eye. We present the first pediatric case of a homozygous mutation c.187G>C p. in two brothers aged 6 and 16 years old. In the complete analysis of the BEST1 gene in the one boy, there was detection of homozygous mutation c.187G>C p. (Glu63Gln). Identical findings were noted in the clinically also affected brother. Both parents are from Kayseri, Turkey, and ophthalmologically healthy. The 75-year-old grandfather of the brothers has late manifestation of blindness since the age of 10, with onset of visual deterioration from the age of 45. The methodological analysis was DNA extraction from EDTA blood. PCR amplification of exon 3 of the BEST1 gene includes adjacent intron regions from generic DNA and subsequent analysis by double-stranded sequencing. The analysis and sequence alignment to the reference (ENST00000378043.9) was performed using the software "Sequence Pilot". The databases dbSNP, ExAc, gnomAD, HGMD and Uni Prot, as well as the prediction programs Predict SNP, Poly Phen 2, SIFT, SNAP, MAPP, PhDSNP, Poly Phen 1 and panther were used for the evaluation of variants. This analysis failed to detect low-grade mosaics, larger delegations or duplications and rearrangements, and mutations outside the regions of the BEST1 gene examined. If a patient

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with a clinical picture of ARB has both parental alleles (gene copies) of BEST1 mutated, so-called bi-allelic mutation status, and there is no ocular symptomatology in the parents, the diagnosis of ARB is very likely [2-5]. The diagnosis should then be confirmed by a supplementary family analysis. The clinical expression of identical genetic disposition can be quite variable, probably due to secondary developments in the wake of the gene mutation, such as neovascularization, glaucoma, extent of the macula, amblyopia in strabismus and glaucoma at least partially suitable to treat ARB [2-5]. The mutation in BEST1 found in the two brothers does not seem to have been described yet in world literature. Therefore, prognostic recommendations of course and treatability for the two children are limited. If the presumed homozygosity for the putative pathogenic BEST1 mutation in the two brothers can be indirectly confirmed by family analysis, this would further confirm the diagnosis [2-5]. Furthermore, it can be assumed that the future children of the brothers will only be at increased risk for ARB if their future partners also happen to be conductors of a pathogenic BEST1 mutation. If the partner is not from the family, i.e., no partnership with blood relatives is entered into, this risk is very low. In conclusion, ARB is an extremely rare disease in childhood, especially in brothers. This is the first case of a new homozygous BEST mutation of two brothers with ARB in world literature to date.

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Conflict of Interest

None to declare.

Informed Consent

Not applicable.

Author Contributions

SB wrote the article, GV and AW checked the article and checked the references, and LB checked also the references in the text and grammatical format.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

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